



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/107, 47/22	A1	(11) International Publication Number: WO 96/36316 (43) International Publication Date: 21 November 1996 (21.11.96)
(21) International Application Number: PCT/US96/07155 (22) International Filing Date: 17 May 1996 (17.05.96) (30) Priority Data: 08/445,242 19 May 1995 (19.05.95) US (71) Applicant: ABBOTT LABORATORIES [US/US]; Chad 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-3500 (US). (72) Inventors: LIPARI, John, M.; 6600 Apollo Drive, Racine, WI 53406 (US). McCHESNEY-HARRIS, Lisa, L.; 105 Lancaster Place, Vernon Hills, IL 60061 (US). MEYER, Glenn, A.; 6712 Pearwood Court, Wilmington, NC 28405 (US). WIELAND, John, J.; 922 Warwick Lane, Libertyville, IL 60048 (US). (74) Agents: DANCKERS, Andreas, M. et al.; Abbott Laboratories, CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-3500 (US).		(81) Designated States: CA, JP, MX, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: SELF-EMULSIFYING FORMULATIONS OF LIPOPHILIC DRUGS		
(57) Abstract Self-emulsifying pharmaceutical pre-concentrate compositions comprising: (a) a lipophilic medicinal compound, (b) d-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS), and (c) a lipophilic phase as well as pharmaceutical compositions comprising such pre-concentrates in combination with a sufficient amount of water to produce a stable emulsion.		

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SELF-EMULSIFYING FORMULATIONS OF LIPOPHILIC DRUGS

Technical Field

This invention relates to pharmaceutical compositions of medicinal compounds, and in particular to spontaneously self-emulsifying pre-concentrates of lipophilic compounds the uses of which include (but are not limited to) the preparation of liquid oral formulations, soft elastic or other capsule formulations for oral delivery, topical formulations for local delivery, suppository formulations, and eye- and ear-drop formulations.

Background of the Invention

Pharmaceutical compounds which are highly lipophilic present considerable formulation challenges. Because of their low solubility in aqueous media (including the contents of the mammalian digestive tract), they often suffer from poor or irregular bioavailability when given orally or via other routes requiring transmembrane absorption.

One method of formulating lipophilic compounds is to combine them with glyceride carriers which form emulsions upon mixing with water. Emulsions are described, for example, in the United States patent issued to Cavanak on June 14, 1983 (Patent No. 4,388,307), a commercial example of which is the oral cyclosporin-containing product SANDIMMUNE. This product comprises the emulsifier LABRAFIL (transesterified triglyceride), olive oil and alcohol in a ratio of approximately 36:52:12, the drug cyclosporin A being present at a concentration of 100 mg/ml. It is suggested in the Cavanak patent that such glyceride carriers may assist in alleviating problems of physical instability (*e.g.*, precipitation of drug from solution), and may also enable higher plasma concentrations.

More recently, it has been proposed that a preferred vehicle for lipophilic compounds is the so-called self-emulsifying drug delivery system which, when exposed to an aqueous medium, forms a fine oil-in-water emulsion with little or no agitation. The property of self-emulsification permits such formulations to be administered as "pre-concentrates" (that is, in concentrated form, as for example in a gelatin or soft elastic capsule) with the expectation that a fine emulsion will be formed in the digestive tract. Moreover, it has been suggested that self-emulsifying formulations, when given orally, may offer improvements in both the rate and extent of absorption of the medicinal compound and also the consistency of the resulting plasma concentration profiles. (*See S. A. Charman et al.*, *Pharmaceutical Research* 9(1):87-93 (1992), and *N. H. Shah et al.*, *International Journal of Pharmaceutics* 106:15-23 (1994).) Additionally, emulsions which have been prepared by combining a self-emulsifying pre-concentrate with an aqueous

medium appear to benefit from improved physical stability when compared with conventional emulsions.

Previously-disclosed self-emulsifying systems include those in which a lipophilic drug is combined with mixtures of (i) medium-chain triglyceride oils and nonionic surfactants,

(ii) vegetable oils and nonionic emulsifiers such as polyglycolized glycerides or medium-chain mono- and diglycerides, or (iii) vegetable oils and nonionic surfactants such as polysorbate 80 or PEG-25 glyceryl trioleate. Other formulations which have been characterized as self-emulsifying, such as the above SANDIMMUNE cyclosporin formulation, additionally contain a substantial amount of ethanol as a solubilizing agent or solvent; however, these solvent-containing preparations are often unsuitable for certain uses, such as filling into gelatin capsules from which the solvent can readily escape.

Improved self-emulsifying formulations, which seek to overcome this drawback, are proposed in the United States patent issued to Hauer *et al.* on August 30, 1994 (Patent No. 5,342,625); in these formulations, a "microemulsion pre-concentrate" of cyclosporin is formed by combining the drug with (i) a hydrophilic phase, (ii) a lipophilic phase, and (iii) a surfactant, as well as optional thickeners, anti-oxidants or other excipients. Despite this, there remains a need for improved formulations of lipophilic drugs which (i) are self-emulsifying and therefore have the advantage of simplicity of use and (ii) comprise excipients that are physiologically well-tolerated. There also remains a need for self-emulsifying pharmaceutical compositions which contain little or no alcohol, which can tolerate a wide range of temperatures and other conditions, and which therefore can be administered orally in pre-concentrate form via gelatin or other capsules or by parenteral means in instances where alcohols may be unduly irritating or incompatible with other formulating vehicles.

Summary of the Invention

It has now been found that the nutritional supplement d-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS), a water-miscible form of vitamin E, can be used to prepare pre-concentrates which spontaneously self-emulsify upon addition to water or other aqueous media. These pre-concentrates permit the oral delivery of lipophilic drugs in a form which, presumably because of the stability and homogeneity of the resulting aqueous emulsion, provides good and unexpectedly consistent bioavailability.

Previously, TPGS has been employed as an emulsifier for lipophilic compounds, a solubilizer of hydrophilic compounds in fats and oils, and as an enhancer of oral bioavailability (when coadministered with, for example, vitamin D or cyclosporin);

however, such earlier uses gave no indication that TPGS-containing formulations could be either (i) self-emulsifying or (ii) capable of forming stable emulsions of small particle size. Hence, the present finding that TPGS imparts these properties to formulations of highly lipophilic drugs is an unexpected one. Moreover, such formulations have the additional
5 advantage that TPGS is readily tolerated, or even beneficial, when given orally or topically.

Accordingly, in one aspect of the present invention are disclosed spontaneously self-emulsifying pharmaceutical pre-concentrate compositions comprising (a) a lipophilic medicinal compound, (b) d-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS), and (c) a lipophilic phase. Preferred pre-concentrates are those in which the TPGS is
10 present in an amount of between about 0.1% and about 50% by weight; more preferred are those in which the TPGS is present in an amount of between about 0.5% and about 15% by weight; and most preferred are those in which the TPGS is present in an amount of between about 1% and about 5% by weight.

Lipophilic phase components which are suitable for use in the above pre-
15 concentrates include (a) fatty acid esters of glycerol, (b) fatty acid esters of propylene glycol, and (c) vegetable oil. Preferably, the weight ratio between such lipophilic phase components and TPGS is between about 1:1 and about 999:1; more preferably, the weight ratio between the lipophilic phase and TPGS is between about 9:1 and about 99:1.

Particular lipophilic phase component which may be used in the pre-concentrates of
20 the present invention include, but are not limited to, propylene glycol laurate (PGL), caprylic/capric triglyceride (such as NEOBEE M-5 oil, a widely-used commercial product), propylene glycol dicaprylate/dicaprate, corn oil, sesame oil and cottonseed oil, either alone or in combination. When PGL is used, a weight ratio between PGL and TPGS of about 15:1 is preferred. Alternatively, when the lipophilic phase comprises propylene glycol
25 laurate and caprylic/capric triglyceride together, a weight ratio between the lipophilic phase and TPGS of between about 20:1 and about 85:1 is preferred; particularly preferred embodiments of such pre-concentrates include those which, when the weight ratio between the PGL and caprylic/capric triglyceride is about 2:1, have a weight ratio between the lipophilic phase and TPGS of about 25:1 or of about 80:1. As a further alternative, when
30 the lipophilic phase comprises propylene glycol dicaprylate/dicaprate, a weight ratio between the lipophilic phase and TPGS of between about 1:1 and about 99:1 is preferred.

The pre-concentrates of the present invention may optionally comprise ethanol as well. When present, the ethanol is preferably used in an amount of between about 1% and about 9% by weight, with an amount of about 5% by weight being especially preferred.

35 As to any of the above pre-concentrates, a preferred medicinal compound for use therein is cyclosporin. Preferred cyclosporin-containing compositions are those in which

the drug is present in an amount of between about 0.5% and 25% by weight; more preferred are those in which the drug is present in an amount of between about 10% and about 15%, with a cyclosporin concentration of about 10% being especially preferred.

In another aspect of the present invention are disclosed pharmaceutical compositions, comprising one of the above self-emulsifying pre-concentrates of the invention in combination with a sufficient amount of water to produce a stable emulsion. Stable emulsions, in which the emulsion particle size is relatively independent of the proportions of internal (lipophilic) and external (aqueous) phases, may be obtained with lipophilic-to-aqueous phase ratios of up to 1:10 or even higher.

Detailed Description of the Invention

As used throughout this specification and in the appended claims, the following terms have the meanings specified:

The term "cyclosporin" as used herein refers to one or more of the cyclosporins and especially to cyclosporin A, as described in the United States patent issued to Härril *et al.* (Patent No. 4,117,118) and incorporated herein by reference.

The term "emulsion" as used herein refers to a dispersion of fine droplets of a lipophilic phase in an aqueous phase, which droplets are stabilized at their lipophilic phase/aqueous phase interface by TPGS.

The term "pre-concentrate" as used herein refers to pharmaceutical compositions or formulations of sufficiently high concentration such that they may be administered directly (as for example when filled into gelatin capsules) or used as a "pre-mix" for preparation of a more dilute formulation (as for example in the form of an emulsion suitable for oral administration).

The term "self-emulsifying" as used herein refers to pre-concentrates which spontaneously or with only minimal agitation form a stable emulsion or dispersion upon being added to an aqueous medium.

The term "stable" as used herein in connection with emulsions refers to emulsions which exhibit no phase separation when kept, without agitation, at room temperature for one hour or longer.

The compositions of the present invention may be administered orally, parenterally (as by intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection or infusion) or topically (as by ointments, drops or transdermal patches), as known in the pharmaceutical arts. Oral formulations include gelatin capsules into which the pre-concentrates of the invention have been filled directly, as well as

emulsions of the invention which are formed by combination of such a pre-concentrate with a suitable aqueous medium such as water. As necessary, the oral formulations may also include adjuvants such as viscosity inducers (for example, microcrystalline cellulose or beeswax); wetting, sweetening, flavoring and/or perfuming agents; and such other inert and pharmaceutically acceptable excipients as may be desired. Solvents may also be included to facilitate dissolution of the drug in the lipophilic phase and/or to prevent congealing of the pre-concentrate; such solvents include, but are not limited to, ethanol, propylene glycol and dimethyl isosorbide and their pharmaceutically acceptable alternatives.

Parenteral formulations may be prepared from emulsions of the present invention, and may contain standard adjuvants as for buffering or control of tonicity. Topical formulations, which are intended for administration to the skin or mucosa (such as the surfaces of the lung and eye), may be prepared from both the pre-concentrates and the emulsions of the invention, and may also contain excipients such as those which modify consistency and rate of absorption. Any of the above formulations, when prepared using the pre-concentrates or emulsions of the present invention, may additionally include antibacterial or antifungal agents, as for example paraben, chlorobutanol, phenol, sorbic acid and the like.

When used in the treatment of disease, the pre-concentrates and emulsions of the present invention may be administered in a sufficient amount, and for a sufficient period of time, as is necessary to provide the desired therapeutic effect. The specific therapeutically effective dose level for any particular patient, which will be determined by the attending physician, will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the medicinal compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well-known in the medical arts.

The pre-concentrates of the invention may be prepared using readily-available materials and equipment. Typically, the lipophilic phase (such as propylene glycol laurate, or PGL and caprylic/capric triglyceride in combination) is warmed to approximately 40-45 °C, with mixing if necessary, before addition of the appropriate amount of TPGS. The combined materials are mixed until dissolved, and the resulting mixture is cooled to room temperature. Depending on its stability and its solubility in the lipophilic phase, the

medicinal agent may be added before or after cooling, followed by mixing until the drug is fully dissolved. If any PGL or lipophilic phase component has been reserved, it is then added with mixing until uniform. The resulting pre-concentrate, which at room temperature may range in consistency from a solution to a soft, waxy, homogenous solid, may then be stored as is, filled into soft gelatin capsules or other capsules, or processed into an aqueous pharmaceutical composition of the present invention by mixing with water or other aqueous liquid.

The formulations of the present invention will be better understood in connection with the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention. Both below and throughout the specification, it is intended that citations to the literature are expressly incorporated by reference.

Example 1

Preparation Of Placebo Pre-Concentrates and Emulsions

The ability of TPGS to facilitate self-emulsification of a lipophilic phase in water was tested by preparing a number of pre-concentrates of the present invention, mixing each one with water, and observing the resulting physical behavior (such as dispersibility and particle size). The specific pre-concentrates were prepared as follows:

(A) Propylene glycol laurate (Gattefossé, Westwood, New Jersey; 71.0-99.9% by weight) was warmed to approximately 40-45°C, and a corresponding amount of TPGS (Eastman Kodak, Tennessee; 29.0-0.1% by weight) was added with mixing until dissolved. The solutions were allowed to cool to room temperature. 100 mg of each pre-concentrate were added to 10 mL of filtered, distilled water, and the resulting mixtures were observed.

(B) Propylene glycol laurate (80.0-92.0% by weight) was warmed to approximately 40-45°C, and a variable amount of TPGS (13.3-1.3% by weight) were added with mixing until dissolved. The solutions were allowed to cool to room temperature, ethanol (6.7% by weight) was added, and the solutions were mixed until uniform. 100 mg of each pre-concentrate were added to 10 mL of filtered, distilled water, and the resulting mixtures were observed.

(C) Propylene glycol laurate (53.3-80.0% by weight) was combined with caprylic/capric triglyceride (NEOBEE M-5 brand; 45.3-6.7% by weight). The mixture was warmed to approximately 40-45°C, and a variable amount of TPGS (1.3-13.3% by weight) was added with mixing until dissolved. The solutions were allowed to cool to room

temperature. 100 mg of each pre-concentrate were added to 10 mL of filtered, distilled water, and the resulting mixtures were observed.

(D) Propylene glycol laurate (46.7% by weight) was combined with caprylic/capric triglyceride (NEOBEE M-5 brand; 33.3% by weight). The mixture was warmed to approximately 40-45 °C, and TPGS (13.3% by weight) was added with mixing until dissolved. The solution was allowed to cool to room temperature, ethanol (6.7% by weight) was added, and the solution was mixed until uniform. 100 mg of the pre-concentrate were added to 10 mL of filtered, distilled water, and the resulting mixture was observed.

(E) Caprylic/capric triglyceride (NEOBEE M-5 brand; 80.0-99.9% by weight) was warmed to approximately 40-45°C, and a corresponding amount of TPGS (20.0-0.1% by weight) was added with mixing until dissolved. The solutions were allowed to cool to room temperature. 100 mg of each pre-concentrate were added to 10 mL of filtered, distilled water, and the resulting mixtures were observed.

(F) Caprylic/capric triglyceride (NEOBEE M-5 brand; 75.0-94.9% by weight) was warmed to approximately 40-45°C, and a variable amount of TPGS (20.0-0.1% by weight) was added with mixing until dissolved. The solutions were allowed to cool to room temperature, ethanol (5.0 or 6.3% by weight) was added, and the solutions were mixed until uniform. 100 mg of each pre-concentrate were added to 10 mL of filtered, distilled water, and the resulting mixtures were observed.

(G) Corn oil, sesame oil, or cottonseed oil (Arista Industries, Inc., Darien, CT; 85.0-94.0% by weight) were warmed to approximately 40-45°C, and variable amounts of TPGS (10.0-0.1% by weight) were added with mixing until dissolved. The solutions were allowed to cool to room temperature, ethanol (5.0% by weight) was added, and the solutions were mixed until uniform. 100 mg of each pre-concentrate were added to 10 mL of filtered, distilled water, and the resulting mixtures were observed.

In each instance (A) through (G), the resulting pre-concentrates readily formed stable aqueous emulsions without the need for vigorous agitation, microfluidizing or other handling commonly associated with the preparation of oil-in-water emulsions. Moreover, particle size distributions were measured for several of the above emulsions. The results, shown below in Table 1, demonstrate that aqueous emulsions formed from pre-concentrates of the present invention have particle sizes that are compatible with the oral delivery of lipophilic drugs.

Table 1
Particle Sizes of Emulsions Formed from Placebo Pre-Concentrates

<u>Proportion (% by weight)</u>				<u>Median Size (μm)</u>
<u>PGL</u>	<u>TPGS</u>	<u>CCT</u>	<u>EtOH</u>	
90	10	---	---	7.7
53.3	13.3	33.3	---	2.8
46.7	13.3	33.3	6.7	8.8

5 PGL = Propylene glycol laurate
 TPGS = d-Alpha-tocopheryl polyethylene glycol 1000 succinate
 CCT = Caprylic/capric triglyceride
 EtOH = Ethanol

Example 2

Preparation Of Pre-Concentrates and Emulsions Containing Cyclosporine A

10 Propylene glycol laurate (65.0-74.0% by weight) was warmed to approximately 40-45°C, and a variable amount of TPGS (10.0-1.0% by weight) was added with mixing
 15 until dissolved. The solutions were allowed to cool to room temperature, and cyclosporine A USP (25.0% by weight) was added and mixed until dissolved. 100 mg of each pre-concentrate were added to 10 mL of filtered, distilled water, and the physical stabilities and particle size distributions of the resulting mixtures were observed. In each case, the pre-concentrates readily formed stable emulsions comparable to those described in the previous
 20 example.

Example 3

Oral Bioavailability of Cyclosporine-Containing Pre-concentrates

25 The oral bioavailability of two pre-concentrates of the present invention was evaluated in fasted beagle dogs as follows: To prepare the first pre-concentrate containing 100 mg/mL cyclosporine, approximately 1.5 mL of propylene glycol laurate (PGL) were added to 1.25 mL caprylic/capric triglyceride (CCT). After warming the mixture to 40-45°C, 0.25 g TPGS was added and dissolved with stirring, and the mixture was cooled
 30 to ambient temperature. 0.50 g of cyclosporine A was then added and dissolved with stirring, after which additional PGL (approximately 1.5 mL) was added and mixed until

uniform to produce a solution containing 25% CCT, 5% TPGS and 10% cyclosporine by weight; the resulting pre-concentrate was designated "Formula 1".

To prepare the second pre-concentrate, also containing 100 mg/mL cyclosporine, approximately 1500 mL of PGL was poured into a vessel and warmed to 40-45°C. 100 g of TPGS were then added and dissolved with stirring, and the mixture was cooled to ambient temperature. 200 g of cyclosporine A were added and dissolved with stirring, after which additional PGL (approximately 200 mL) was added and mixed until uniform to produce a solution containing 5% TPGS and 10% cyclosporine by weight; the resulting pre-concentrate was designated "Formula 2".

The above pre-concentrates, and control samples consisting of the commercial cyclosporine product SANDIMMUNE, were then filled into soft elastic capsules in quantities which, when delivered to the subjects, delivered 5 mg/kg cyclosporine to each dog. The capsules were heat-sealed and inspected to confirm the absence of leakage.

Three groups of six dogs each were fasted overnight and then, at time 0, were given one of the above encapsulated pre-concentrates. Blood samples were taken at 15, 30, 60 and 90 minutes and at 2, 4, 6, 9, 12, 15 and 24 hours after dosing, and analyzed for the blood concentration of cyclosporine. (Food was made available after blood had been drawn at the 12-hour mark.) From these data, the maximum serum concentration (C_{max}), time from dosing until the maximum concentration (T_{max}) and total presence (area under curve, or AUC) as well as the respective standard deviations were computed, and are shown below in Table 2.

Table 2
Blood Concentrations of Cyclosporine After 5 mg/kg Oral Dosing of Dogs

<u>Formulation</u>	<u>C_{max} (ng/mL)</u>	<u>T_{max} (hours)</u>	<u>AUC (ng•hour/mL)</u>
Formula 1	405 ± 43	1.7 ± 0.4	2723 ± 587
Formula 2	631 ± 121	1.4 ± 0.4	3532 ± 899
Control	672 ± 157	1.2 ± 0.3	2808 ± 656

These results demonstrate that cyclosporine formulated as a pre-concentrate of the present invention is readily bioavailable, and has a pharmacokinetic profile substantially similar to that of the commercial cyclosporine product. Moreover, the variability (standard deviation) of maximum serum concentration obtained with the pre-concentrates of the present

invention can be seen to be less in each case than that observed using the commercial control.

Example 4

5 Preparation Of Pre-Concentrates Containing Cyclosporine A and Ethanol

Four additional pre-concentrates of the present invention were prepared for further study in clinical trials, according to the following formulations (in which the percentages indicated are by weight):

10

(A): 75% propylene glycol laurate
5% TPGS
5% ethanol
15% cyclosporine

15

(B): 54% propylene glycol laurate
25% caprylic/capric triglycerides
1% TPGS
5% ethanol
20 15% cyclosporine

20

(C): 52% propylene glycol laurate
25% caprylic/capric triglycerides
3% TPGS
25 5% ethanol
15% cyclosporine

25

(D): 50% propylene glycol laurate
25% caprylic/capric triglycerides
30 5% TPGS
5% ethanol
15% cyclosporine

30

35 In each instance (A) through (D) above, the pre-concentrates were prepared as described in the previous examples, and were observed to have satisfactory physical characteristics both before and after addition to water.

40 It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined solely by the appended claims and their equivalents. It is expected that various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art, and may be made without departing from the spirit and scope thereof.

What is claimed is:

1. A self-emulsifying pharmaceutical pre-concentrate composition comprising
 - (a) a lipophilic medicinal compound,
 - (b) d-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS), and
 - (c) a lipophilic phase.
2. A self-emulsifying pre-concentrate according to Claim 1 wherein the TPGS is present in an amount of between 0.1% and 50% by weight.
3. A self-emulsifying pre-concentrate according to Claim 2 wherein the TPGS is present in an amount of between 1% and 5% by weight.
4. A self-emulsifying pre-concentrate according to Claim 1 wherein the lipophilic phase comprises at least one component selected from the group consisting of
 - (a) fatty acid esters of glycerol,
 - (b) fatty acid esters of propylene glycol, and
 - (c) vegetable oil.
5. A self-emulsifying pre-concentrate according to Claim 4 wherein the weight ratio between the lipophilic phase and TPGS is between 1:1 and 999:1.
6. A self-emulsifying pre-concentrate according to Claim 5 wherein the weight ratio between the lipophilic phase and TPGS is between 9:1 and 99:1.
7. A self-emulsifying pre-concentrate according to Claim 4 wherein the lipophilic phase comprises propylene glycol laurate and wherein the weight ratio between the propylene glycol laurate and TPGS is about 15:1.
8. A self-emulsifying pre-concentrate according to Claim 4 wherein the lipophilic phase comprises propylene glycol laurate and caprylic/capric triglyceride, and wherein the weight ratio between the lipophilic phase and TPGS is between 20:1 and 85:1.
9. A self-emulsifying pre-concentrate according to Claim 8 wherein the weight ratio between the propylene glycol laurate and caprylic/capric triglyceride is about 2:1.

10. A self-emulsifying pre-concentrate according to Claim 9 wherein the weight ratio between the lipophilic phase and TPGS is between 25:1 and 80:1.
11. A self-emulsifying pre-concentrate according to Claim 4 wherein the lipophilic phase comprises propylene glycol dicaprylate/dicaprate, and the weight ratio between the lipophilic phase and TPGS is between 1:1 and 99:1.
12. A self-emulsifying pre-concentrate according to any of claims 4 to 11 additionally comprising ethanol in an amount of between 1% and 9% by weight.
13. A self-emulsifying pre-concentrate according to any of claims 1 to 12 wherein the medicinal compound is cyclosporin and wherein the cyclosporin is present in an amount of between about 0.5% and about 25% by weight.
14. A self-emulsifying pre-concentrate according to Claim 13 wherein the cyclosporin is present in an amount of between about 10% and about 15% by weight.
15. A pharmaceutical composition comprising a self-emulsifying pre-concentrate according to Claim 13 in combination with a sufficient amount of water to produce a stable emulsion.
16. A pharmaceutical composition comprising a self-emulsifying pre-concentrate according to any of claims 1-12 in combination with a sufficient amount of water to produce a stable emulsion.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/107 A61K47/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 120, no. 26, 27 June 1994 Columbus, Ohio, US; abstract no. 330990, XP002013044 cited in the application see abstract & INT. J. PHARM., vol. 106, no. 1, 1994, pages 15-23, N. H. SHAH ET AL.: "SELF-EMULSIFYING DRUG DELIVERY SYSTEMS (SEDDS) WITH POLYGLYCOLYZED GLYCERIDES FOR IMPROVING IN VITRO DISSOLUTION AND ORAL ABSORPTION OF LIPHILIC DRUGS" --- -/--	1-16

☒ Further documents are listed in the continuation of box C.

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A	<p>FR,A,2 636 534 (SANDOZ) 23 March 1990 cited in the application see the whole document -----</p>	1-16

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